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| EXAMINER | |
|---|---|
| KAPUSHOC, STEPHEN THOMAS | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/803,180 | CARGILL ET AL. | |
| | Examiner | Art Unit | |
| | Stephen Kapushoc | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *36,39-45,56 and 59-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,39-45,56 and 59-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 36, 39-45, 56 and 59-74 are pending and examined on the merits.

1. Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 07/07/2008.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

### *New Claim Rejections - 35 USC § 112*

2. Claim 74 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 74 requires 'determining the identity of the single nucleotide polymorphism (SNP) rs2276864', where the term 'rs2276864' does not appear to be a part of, or defined by, the specification as originally filed. While Applicants state that basis for the new claim may be found in the specification, and Tables 1, 2, 5, and 6 and the sequence listing, the Examiner's review of the specification did not identify the newly added term within the specification. While the specification does provide particular sequences, there is no indication in the specification of the relationship of the

sequences and any of the information that may be accessible in a database as 'rs2276864'. As such, the limitations of the claims are new matter.

***New Claim Rejections - 35 USC § 112 1st ¶ - Written Description due to Improper Incorporation by Reference***

3. Claim 74 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 74 requires 'determining the identity of the single nucleotide polymorphism (SNP) rs2276864', where the nucleic acid sequence context of the reference SNP (rs) is critical for the practice of the claimed method. However, in the instant case the attempt by Applicant to incorporate the essential subject matter of a particular polymorphic position at within a specific nucleic acid sequence context as a claim limitation is not effective.

37 CFR 1.57 (c) provides that:

> c) "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:
>
> (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor

> of carrying out the invention as required by the first paragraph of 35 U.S.C. 112

In the instant case, the essential subject material is provided in the claim bf reference to a dbSNP ReferenceSNP entry, which is not an acceptable reference under 37 CRF 1.157(c) for essential subject matter. The NCI website notes, with regard to the removable nature of rs entries:

> Approximately 8% percent of the rs numbers in dbSNP have been retired since the inception of dbSNP, so you could say that rs numbers are not entirely stable. Any rs number in dbSNP could retire for one of the following reasons:
> 1. rs numbers occasionally merge with other rs numbers because they are found to map to the same location on the genome. When such a merge happens, ss numbers of the higher rs number are reassigned to the lower rs number, and the higher rs number is retired.
> 2. If all ss numbers in an rs cluster are withdrawn, then the corresponding rs number is retired.
> 3. We break an existing cluster and re-instantiate a retired rs number based on a reported conflict from a dbSNP user (a rare occurrence).

Thus it is established that any rs entry, such as the rs2276864 of the rejected claim, can be removed from the database such that the requirements of the claimed method will be modified.

In the instant case, the rejection may be overcome if the phrase 'determining the identity of the single nucleotide polymorphism (SNP) rs2276864' is amended to recite 'determining the identity of the nucleotide at position 101 of SEQ ID NO: 5502'

***Withdrawn Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness***

4. The rejection of claims 36, 39-45, 56, and 59-65 under 35 U.S.C. 112, second paragraph, as being indefinite, as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendments to the claims.

***Withdrawn Claim Rejections - 35 USC § 112 1st - Written Description***

5. The rejection of claims 1 and 29-35 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, as set forth in the previous Office Action, is **WITHRAWN** in light of the cancellation of claims 1 and 29-35.

***Maintained Claim Rejections - 35 USC § 112 1st¶ - Scope of Enablement***

6. Claims 36, 39-45, 56 and 59-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification:

While being enabling for,

> A method for identifying a human individual who has a decreased risk for developing positive autoantibody rheumatoid factor (RF+) rheumatoid arthritis (RA) comprising:
> obtaining a biological sample from said individual wherein the biological sample comprises nucleic acids; and
> detecting the nucleotide content at position 101 of SEQ ID NO: 5502 or the complement of SEQ ID NO: 5502 in said nucleic acids;
> wherein, detecting the nucleotide A at position 101 of SEQ ID NO: 5502, or detecting the nucleotide T at position 101 of the complement of SEQ ID NO: 5502, identifies the individual as having a decreased risk for developing RF+ RA.

Or

> A method for identifying a human individual who has an increased risk for developing positive autoantibody rheumatoid factor (RF+) rheumatoid arthritis (RA) comprising:
> obtaining a biological sample from said individual wherein the biological sample comprises nucleic acids; and
> detecting the nucleotide content in both alleles at position 101 of SEQ ID NO: 5502 or the complement of SEQ ID NO: 5502 in said nucleic acids;
> wherein, detecting the nucleotide G at position 101 of both alleles of SEQ ID NO: 5502, or detecting the nucleotide C at position 101 of the complement of both alleles of

SEQ ID NO: 5502, identifies the individual as having an increased risk for developing RF+ RA.

does not reasonably provide enablement for methods comprising determining the presence of a C at position 101 of SEQ ID NO: 5502 (as encompassed by independent claims 36 and 56), or identification methods comprising determining the presence of T of C at position 101 of SEQ ID NO: 5502 or A or G at position 101 of the complement of SEQ ID NO: 5502, as appear to be encompassed by the claims, or the detection of A in rs2276864. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

**Nature of the invention and breadth of the claims**

The claims of the instant application are drawn to methods for identifying an individual who has an altered risk for developing RA.

The recitation of detected nucleotide content in the rejected claims contains language encompassing the detection of content at a polymorphic position or the detection of the complement of that content; and the claims encompass the detection of the content in a sequence context, or the complement of the sequence content. However, there is not a clear limitation in the claims to what content is required to be detected in any particular context. For example in independent claim 36, the claim encompasses 'position 101 of SEQ ID NO: 5502 or its complement', and encompasses 'the presence of C or its complement'.

The claims encompass the identification of increased RF+ RA risk with any detection of the C allele, and the identification of decreased RF+ RA risk with any detection of the T allele.

The nature of the invention requires knowledge of an association between broadly claimed nucleic acid content and altered risk of having RA.

**Direction provided by the specification and working example**

The instant specification teaches that an association study of a SNP and a specific disorder involves determining the presence or frequency of the SNP allele in biological samples from individuals with the disorder (i.e. cases) of interest and comparing the information to that of control individuals who do not have the disorder (p.7 ln.28 – p.8 ln.4).

The instant specification provides an example of an association study of the polymorphic content at position 101 of SEQ ID NO: 5502, which may be either an A or a G, and is also identified as hCV163035 and known in the art as rs2276864. The specification teaches that the frequency of the particular allele was analyzed in two (p.120 ln.26 – p.121 ln.11) patient populations: a Discovery Set (475 unrelated cases and 475 controls who were RF+); and a Replication Set (840 cases from 463 families and 926 controls). The specification further indicates that the Replication set was analyzed in totality (i.e. an 'all' stratum) after stratification of the subjects into an RF+ stratum (p.12; p.121 ln.28).

The specification teaches the specific association of the A allele (i.e. an A nucleotide a position 101 of SEQ ID NO: 5502) with a decreased risk of RA as the A

allele is found at a significantly higher frequency in control samples in the Discovery Set and the Replication Set (Table 6). It is noted that Table 6 designates the 'T' allele as associated with the decreased risk of RA, and the specification indicates that nucleotide content may be described as the reverse of the nucleotide content at the position (e.g. p.20, lns.25-30), thus the T allele of the reverse complement of SEQ ID NO: 5502 is the A allele of SEQ ID NO: 5502. The analysis of the Discovery Set is an analysis of RF+ RA, because as stated in the specification all cases of the Discovery Set were RF+ (p.120 ln.29). While the instant specification provides that the A allele is indicative of a decreased risk for RA in the Replication Set in the 'All' Stratum, the specification provides no indication as to how many of the cases in the Replication Set were either RF+ or RF- (i.e. while the specification indicates that the Replication Set had 840 patients, it is not known if there were enough of both RF+ and RF- individuals to make data regarding the 'All' stratum significant for both RF+ and RF-). Thus it is not possible to determine from the data of Table 6 indicating a significant relationship between the A allele of SEQ ID NO: 5502 and decreased risk of RA is in fact significant within the RF- population of cases under analysis. Thus while the data of specification teaches an association of the A allele with decreased risk of RF+ RA, it is not clear from the specification if the A allele is specifically associated in the same way, or in a significant fashion, with RF- RA.

Because the claims do not clearly specify the detection of homozygous G content at position 101 of SEQ ID NO: 5502 in the determination of increased risk of RF+ RA (it is noted that independent claims 36 and 56 do not require analysis of both alleles of

SEQ ID NO: 5502), where determination of heterozygosity at the position (i.e. an individual with one of each allele) would be detection of both alleles, it is relevant to point out that the data presented in the instant specification (i.e. Table 6) indicates only that the presence of a T allele (which is an A allele in SEQ ID NO: 5502) is indicative of a decreased risk of RF+ RA. The data does not stratify the data based on genotype (i.e. CC vs CT vs TT), and thus appears to present only that detection of a T allele (i.e. either in a CT or TT genotype) is indicative of decreased risk of RF+ RA as compared to a CC individual, and does not provide a comparison of the relative risk of RF+ RA in a CT versus a CC individual. Thus while it is possible for the data to support that the presence of an A at position 101 of SEQ ID NO: 5502 is indicative of decreased risk of RF+ RA (because presence of either an AA or AG genotype would have a decreased risk), the data would not support making a determination based only on the presence of a single G allele (because it would not be known if the individual has a GG (increased risk) genotype or an AG (decreased risk) genotype).

The instant specification provides only the association analysis of either an A or a G at position 101 of SEQ ID NO: 5502 (as consonant with the Election), and does not provide any analysis of any other polymorphic content at any other position of SEQ ID NO: 5502. With regard to claim 74, it is noted that the requirement for the recited 'rs2276864' has been rejected previously in this Office Action for issues under 35 112 1$^{st}$. However it is noted that claim 74 recites 'the presence of T or its complement at the SNP', where rs2276864 is a specific SNP (i.e. particular polymorphic content in a

particular context) that is either a T or a C, where the complement of T (as encompassed by the claims) is an A.

**State of the art, level of skill in the art, and level of unpredictability**

While the state of the art and level of skill in the art with regard to the detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach an association between any polymorphism at position 101 in SEQ ID NO: 5502 and altered risk for developing RA. And because the claims encompass the detection of a variety of polymorphic nucleotide content at position 101 of SEQ ID NO: 5502, it is relevant to point out the unpredictability in associating any particular SNP with a particular phenotypic trait. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

**Quantity of experimentation required**

A large amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope of the claims. Such experimentation would include examining an association of any nucleotide content at position 101 of SEQ ID NO: 5502 with the risk of RF+ RA. This would involve large case:control

studies in multiple human populations, and the analysis of different polymorphic variants of SEQ ID NO: 5502, where the specification provides only for the detection of either A or G at position 101 of SEQ ID NO: 5502. Even if such an analysis were to be performed, there is no assurance that one would find any significant associations beyond those specifically taught in the particular example of the instant specification.

**Conclusion**

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the few specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

**Response to Remarks**

Applicants have traversed the rejection of claims under 35 USC 112 1st¶ for lack of enablement. Applicants have argued (p.7-8 of Remarks) that Table 6 of the specification provides that the A allele at the SNP is associated with decreased risk, and thus the A allele provides a decreased risk relative to the risk conferred by the other allele of the same SNP position. The argument is not found to be persuasive. As set forth in the rejection, the data presented in Table 6 is not stratified by genotype, and only provides that in pooled genotype samples the T allele was over represented in the decreased risk population. As such the skilled artisan would recognize that genotypes comprising the T allele (i.e.: T T and T C genotypes at position 101 of the complement of SEQ ID NO: 5502) would have a decreased risk in comparison to individuals with no

T alleles (i.e.: the C C genotype). This issue is clearly seen in the method of independent claim 56, where the method encompasses that the presence of a C is indicative of increased risk, and the presence of a T is indicative of decreased risk. But there is no indication that an individual with both a C and a T (i.e.: the T C genotype) would have both an increased and a decreased risk. There is no analysis in the specification to provide, for example, that there is a level of risk association with genotype whereby risk with C C > T C > T T; the specification treats only the combination of both the T C and T T genotypes in the determination of the T allele as the decreased risk allele. claims have been amended to specifically point out the number of alleles that are required for either increased risk or decreased risk association.

It is noted that with regard to the rejection of claims, the claims specifically require that, for example, the presence of T at position 101 of SEQ ID NO: 5502 is indicative of decrease risk of developing RA, where the specification indicates that position 101 of SEQ ID NO: 5502 may be either an A or a G. While the claims recite the phrase 'or its complement thereof' (e.g. claim 66 recites 'wherein the presence of T at position 101 of SEQ ID NO: 5502 or its complement thereof'), this recitation does not serve to clearly limit the subject matter of the claims to the subject matter enabled by the specification. For example, claim 66 encompass the detection of T at position 101 of SEQ ID NO: 5502, where such detection is not enabled by the specification. If Applicants wish to include language specifying analysis of a sequence complementary to the disclosed sequence, language such as:

detecting the nucleotide A at position 101 of SEQ ID NO: 5502, or detecting the nucleotide T at position 101 of the complement of SEQ ID NO: 5502

may more clearly specify the subject matter enabled by the instant specification. As detailed in the rejection, the data presented in the specification (Table 6) supports only the identification of an A at position 101 of SEQ ID NO: 5502 (i.e. identification of either an AA or AG genotype) as indicative of a decreased risk of RF+ RA); the data does not support the detection of a single G (or C in the complement) allele as indicative of an increased risk of RF+ RA.

The rejection as set forth is **MAINTAINED**.

## *Conclusion*

7. No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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